Regioselectivity in Cross-Coupling Reactions of 2,6,8-Trichloro-9-(tetrahydro-pyran-2-yl)purine: Synthesis of 2,6,8-Trisubstituted Purine Bases

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Received 12 July 2004; revised 16 August 2004

Abstract: The regioselectivity of cross-coupling reactions (Pd-catalyzed Suzuki–Miyaura reactions with phenylboronic acid and Fe-catalyzed reactions with methylmagnesium chloride) of 2,6,8-trichloro-9-(tetrahydro-pyran-2-yl)purine with varying amounts of the organometallic reagent was studied. In general, the regioselectivity of these reactions was quite low giving mixtures of isomers of mono-, di- and trisubstituted products. Nevertheless, 2,6-dichloro-8-methyl-9-THP-purine (1aa), 2-chloro-6,8-dimethyl-9-THP-purine (1ab) and 2,8-dichloro-6-phenyl-9-THP-purine (1ac) were isolated in acceptable yields and used as intermediates for further cross-coupling reactions giving a series of 2,6,8-trisubstituted 9-THP-purines that were deprotected to the corresponding purine bases. Characteristic 13C NMR shifts of CH3 or ipso-Ph carbons in different positions of the purine ring have been observed enabling rapid and facile identification of the particular isomer.

Key words: purines, nucleobases, cross-coupling reactions, iron, palladium

Biological activity and importance of 6-methylpurines1 and 6-phenylpurines2 bases and nucleosides have been reported many times. This led us to the synthesis of their derivatives bearing additional substituents in position 2 or 8 by regioselective cross-coupling reactions3 of 2,6- or 6,8-dihalopurines. In this way, 2- and 8-substituted 6-phenylpurine ribonucleosides,4,5 as well as 2-substituted 6-methylpurines,6 2-substituted 6-phenylpurines,7 8-substituted 6-phenylpurines and 6-substituted 8-methylpurines8 were recently prepared.

2,6,9-Trisubstituted and 2,6,8,9-tetrasubstituted purines (usually bearing N- or O-substituents in the positions 2, 6 and 8) recently attracted attention as inhibitors of CDK,9 estrogen sulfotransferase10 and tubulin polymerization11 and as antagonists of a corticotropin-releasing hormone.12 Combinatorial libraries of these compounds were prepared13 on solid-phase using highly regio- and chemoselective nucleophilic substitutions of dihalopurines with N-, O- or S-nucleophiles. However, a maximum of one C-substituent was introduced by a cross-coupling reaction on the last remaining leaving group at the end of the synthesis. No regioselective cross-coupling was ever used on solid support. This paper reports on regioselectivity of cross-coupling reactions of THP-protected 2,6,8-trichloropurine with varying amounts of phenylboronic acids or methylmagnesium chloride. The aim of this study was to test whether the cross-couplings are suitable for consecutive attachment of three different C-substituents onto purine ring and to prepare 2,6,8-trisubstituted purine bases bearing the prominent methyl and/or phenyl substituents for biological activity screening.

Cross-coupling reactions of 2,6- and 6,8-dihalopurines are chemo- and regioselective.4–8,14 In general, the reactions of 2,6- or 6,8-dichloropurines with one equivalent of an organometallic reagent (arylboronic acid, arylstannane or arylzinc halide) lead to regioselective substitution in position 6. On the other hand, 2- or 8-iodo-6-chloropurines react chemoselectively with organometallic reagents at iodo substituted position 2 or 8. The only exception from these general rules is the recently reported8 Fe-catalyzed reaction of 6,8-dichloropurines with methylmagnesium chloride giving preferentially 6-chloro-8-methylpurines. So far, no study of regioselectivity of cross-coupling reactions of 2,6,8-trichloropurines was reported. Throughout the paper, the purines will be numbered in the form of 1xyz or 2xyz (x denotes substituent in position 2, y in position 6 and z in position 8).

THP-protected 2,6,8-trichloropurine 1aaa was the starting compound of choice since the THP-group is stable under standard cross-coupling conditions (neutral or basic) and readily cleaved by acids. At first, we have tried to prepare 2,6,8-trichloropurine from uric acid by the Fischer deoxochlorination procedure15 (POCl3, N,N-dimethyl-aniline or DMF) but this method was irreproducible in our hands giving complex mixtures. Finally, we have succeeded in a one-pot 8-lithiation/chlorination sequence (Scheme 1) starting from easily available 2,6-dichloro-9-THP-purine (analogous to known16 8-halogenation of 6-halopurines) giving the desired trichloropurine 1aaa in an acceptable yield of 52%.

The protected trichloropurine 1aaa was subjected to a series of cross-coupling reactions: Fe-catalyzed reaction17

![Scheme 1](image-url)
with methylmagnesium chloride and Pd-catalyzed Suzuki–Miyaura reaction\textsuperscript{18} with phenylboronic acid (Scheme 2, Table 1). The molar ratios of \textit{1aaa} and organometallics varied from 1:1 to large excess of the reagent in order to achieve selective mono-, di- or trisubstitution. Unfortunately, both types of reactions appeared to be much less selective than those of 2,6- or even 6,8-dichloropurines giving rather complex mixtures of products and isomers.

In the case of the Grignard reagent, the reaction of \textit{1aaa} with 1–1.5 equivalents of MeMgCl gave conversions of 50–62\% affording chromatographically separable mixtures of 8-methyl- and 6,8-dimethylpurines \textit{1aab} and \textit{1abb} in moderate yields (Table 1, entries 1 and 2) accompanied by inseparable mixture of minor isomers (in both cases substantial amount of the unreacted starting \textit{1aaa} was recovered and reused). When using 2.1 equivalents of MeMgCl, the conversion was higher but the mixture of products even more complex (entry 3). In this case, also minor isomers \textit{1aba} and \textit{1bab} were isolated and characterized. On the other hand, even the use of a large excess (12 equiv) of the reagent did not lead to complete conversion to 2,6,8-trimethylpurine \textit{1bbb} (entry 4). In order to selectively and efficiently prepare the trimethylpurine \textit{1bbb} the Pd-catalyzed reaction with trimethylaluminum\textsuperscript{19} was used giving virtually complete conversion and good yield of \textit{1bbb} (entry 5).

The Suzuki–Miyaura reaction of \textit{1aaa} under Pd(PPh\textsubscript{3})\textsubscript{4} catalysis in toluene with one equivalent of PhB(OH)\textsubscript{2} gave a mixture, from which 2,8-dichloro-6-phenylpurine \textit{1aca} was isolated in a reasonable yield of 46\% (entry 6). The same reaction using an excess of the boronic acids (entries 7 and 8) gave only inseparable complex mixtures containing mono-, di- and triphenylpurines, as well as some products of partial dechlorination. Fractional crystallization of these mixtures gave pure \textit{1ccc} in low yields (ca. 10–20\%), but attempts to isolate any other product in pure form failed. Again, even the use of a large excess of the boronic acid (entry 8) did not lead to complete conversion to the 2,6,8-triphenylpurine \textit{1ccc}. In order to enhance the reactivity we turned our attention to the Lakshman\textsuperscript{18c} modified conditions: Pd(OAc)\textsubscript{2}, 2-(dicyclohexylphosphino)biphenyl (biphenPCy\textsubscript{2}) and K\textsubscript{3}PO\textsubscript{4} in THF. Under these conditions the reaction of \textit{1aaa} with two equivalents of the boronic acid gave again inseparable mixture (entry 9), but the reaction with an excess of PhB(OH)\textsubscript{2} gave finally complete conversion to \textit{1ccc} (entry 10).

Despite the low selectivity and moderate yields, 2,6-dichloro-8-methyl-9-THP-purine (\textit{1aab}), 2-chloro-6,8-dimethyl-9-THP-purine (\textit{1abb}) and 2,8-dichloro-6-phenyl-9-THP-purine (\textit{1aca}) were chromatographically isolated in sufficient amounts and used as intermediates for further cross-coupling reactions. The Suzuki–Miyaura reaction of 2,6-dichloro-8-methylpurine \textit{1aab} with three

\textbf{Scheme 2} Reagents and conditions: i) MeMgCl, Fe(acac)\textsubscript{3}, THP, NMP, r.t.; ii) Me\textsubscript{3}Al, Pd(PPh\textsubscript{3})\textsubscript{4}, THF, 80 °C; iii) PhB(OH)\textsubscript{2}, K\textsubscript{2}CO\textsubscript{3}, Pd(PPh\textsubscript{3})\textsubscript{4}, toluene, 90 °C; iv) PhB(OH)\textsubscript{2}, K\textsubscript{3}PO\textsubscript{4}, Pd(OAc)\textsubscript{2}, biphenPCy\textsubscript{2}, THF, 80 °C
Synthesis of 2,6,8-Trisubstituted Purine Bases

Equivalents of phenylboronic acid under standard conditions in six hours gave selectively the 2-chloro-6-phenyl derivative 1acb in relatively good yield (entry 11), while when using a larger excess and prolonged reaction time (30 hours), the 2,6-diphenyl derivative 1ccb was obtained in very good yield (entry 12). Analogous reaction of 2-chloro-6,8-dimethylpurine 1abb gave the 2-phenyl derivative 1cbb in excellent yield (entry 13). 2,8-Dichloro-6-phenylpurine 1aca reacted with excess of MeMgCl under Fe catalysis to give selectively 8-monomethyl derivative 1acb in good yield, while the reaction with trimethylaluminium gave quantitatively 2,8-dimethyl-6-phenylpurine 1bcb.

Nine examples of THP-protected 2,6,8-trisubstituted purine derivatives 1xyz obtained in sufficient amounts were deprotected under standard conditions (reflux in EtOH in presence of acidic cation exchanger) to give the corresponding free trisubstituted purine bases 2xyz in very good yields of 85–96% (Scheme 3, Table 2).

The regioselectivity of cross-coupling reactions was determined by NMR spectroscopy. H,C-HMBC and DPFG-NOE experiments were performed for all the prepared compounds to verify the position of methyl or phenyl substituents. In the cases where an 8-substituent was present, the NOE signal enhancement for methyl or o-H-Ph was observed after irradiation of the OCH proton from the 9-THP substituent. An assignment of quaternary purine carbons as another tool for determination of the position of substituents was based on the measurement of H,C-long-range correlations of OCH protons of THP (cross-peaks to C-4 and C-8), CH₃ and o-H-Ph protons. For example, the H,C-HMBC spectrum of 6,8-dimethyl-2-phenyl-9-THP-purine 1ccb shows cross-peaks of OCH of THP (5.87 ppm) to C-4 (152.32 ppm) and C-8 (153.26 ppm), of CH₃-8 (2.79 ppm) to C-8 (153.26 ppm), of CH₃-6 (2.86 ppm) to 85–96% (Scheme 3, Table 2).

### Table 1 Cross-Coupling Reactions of Chloropurines 1aaa, 1aab, 1abb and 1aca

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Compd</th>
<th>Reagent</th>
<th>Ratio</th>
<th>Condns*</th>
<th>Products (Yield)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1aaa</td>
<td>MeMgCl</td>
<td>1:1.1</td>
<td>A</td>
<td>1aab (14%), 1abb (11%), recovered 1aaa (50%)</td>
</tr>
<tr>
<td>2</td>
<td>1aaa</td>
<td>MeMgCl</td>
<td>1:1.5</td>
<td>A</td>
<td>1aab (23%), 1abb (16%), recovered 1aaa (38%)</td>
</tr>
<tr>
<td>3</td>
<td>1aaa</td>
<td>MeMgCl</td>
<td>1:2.1</td>
<td>A</td>
<td>1aab (16%), 1abb (36%), 1aab (3%), 1bab (3%), recovered 1aaa (10%)</td>
</tr>
<tr>
<td>4</td>
<td>1aaa</td>
<td>MeMgCl</td>
<td>1:12</td>
<td>A</td>
<td>1abb (40%), 1bcb (57%)</td>
</tr>
<tr>
<td>5</td>
<td>1aaa</td>
<td>Me₃Al</td>
<td>1:6</td>
<td>B</td>
<td>1bcb (80%)</td>
</tr>
<tr>
<td>6</td>
<td>1aaa</td>
<td>PhB(OH)₂</td>
<td>1:1</td>
<td>C</td>
<td>1aca (46%) + complex mixture of other products</td>
</tr>
<tr>
<td>7</td>
<td>1aaa</td>
<td>PhB(OH)₂</td>
<td>1:2</td>
<td>C</td>
<td>inseparable complex mixturec</td>
</tr>
<tr>
<td>8</td>
<td>1aaa</td>
<td>PhB(OH)₂</td>
<td>1:6</td>
<td>C</td>
<td>inseparable complex mixturec</td>
</tr>
<tr>
<td>9</td>
<td>1aaa</td>
<td>PhB(OH)₂</td>
<td>1:2</td>
<td>D</td>
<td>inseparable complex mixturec</td>
</tr>
<tr>
<td>10</td>
<td>1aaa</td>
<td>PhB(OH)₂</td>
<td>1:8.3</td>
<td>D</td>
<td>1ccc (87%)</td>
</tr>
<tr>
<td>11</td>
<td>1aab</td>
<td>PhB(OH)₂</td>
<td>1:3</td>
<td>Cd</td>
<td>1acb (69%)</td>
</tr>
<tr>
<td>12</td>
<td>1aab</td>
<td>PhB(OH)₂</td>
<td>1:4.5</td>
<td>Cn</td>
<td>1cbb (85%)</td>
</tr>
<tr>
<td>13</td>
<td>1abb</td>
<td>PhB(OH)₂</td>
<td>1:4</td>
<td>C</td>
<td>1cbb (96%)</td>
</tr>
<tr>
<td>14</td>
<td>1aca</td>
<td>MeMgCl</td>
<td>1:3</td>
<td>A</td>
<td>1acb (79%)</td>
</tr>
<tr>
<td>15</td>
<td>1aca</td>
<td>Me₃Al</td>
<td>1:4</td>
<td>B</td>
<td>1bcb (98%)</td>
</tr>
</tbody>
</table>

*a Conditions: (A) MeMgCl, Fe(acac)₃, THF, NMP, r.t.; (B) Me₃Al, Pd(PPh₃)₄, THF, 80 °C; (C) PhB(OH)₂, Pd(PPh₃)₄, K₂CO₃, toluene, 90 °C; (D) PhB(OH)₂, Pd(OAc)₂, bipyrenPCy₂, K₃PO₄, THF, 80 °C.

b Isolated yields (average of 2–3 identical experiments).

c Compound 1ccc was isolated by fractional crystallization in low yields (ca. 10–20%).

d Reaction time 6 h.

Scheme 3  i) Dowex 50X8 (H⁺ form), EtOH, reflux
to C-5 (130.53 ppm) and C-6 (156.95 ppm) and of o-H-Ph-2 (8.50 ppm) to C-2 (157.96 ppm). The substitution pattern of each trisubstituted purine 1xyz is apparent just from $^{13}$C NMR shifts of methyl or i-C-Ph carbons (Table 3). The carbon signals of methyl group in the position 8 appear at ca. 16 ppm, in the position 6 at ca. 19, while in the position 2 at ca. 26 ppm for all compounds. Analogously, the ipso-carbons of Ph groups resonate at ca. 130, 134–136 and 138 in the positions 8, 6 and 2, respectively. The same behavior was observed in the series of free purine bases 2xyz and also in previously published $^{2,6}$- and 6,8-disubstituted purines. Free bases 2xyz exhibit tautomerism$^{21}$ that results in very weak and in some cases missing quaternary carbons in $^{13}$C NMR spectra. However, the missing carbons could be in several cases observed indirectly from HMBC spectra.

In conclusion, cross-coupling reactions of 2,6,8-trichloro-9-THP-purine 1aaa proceed with low selectivity but still basically follow the same rules as for 6,8-dichloropurines. The Fe-catalyzed reaction with methylmagnesium chloride occurs preferentially in position 8 while the Suzuki–Miyaura reaction with phenylboronic acid in position 6. It is also quite difficult, and modified methods must be used in order to achieve complete disubstitution. Three types of partly substituted derivatives could be isolated in sufficient amounts and used for another cross-coupling step. On the other hand, cross-coupling reactions of protected 2,6-dichloro-8-methylpurine 1aab and 2,8-dichloro-6-phenylpurine 1aca are regioselective and modified conditions or prolonged reaction times must be used in order to achieve complete disubstitution. Obviously, this methodology is not suitable for regioselective solid-phase synthesis but a series of nine different 2,6,8-trisubstituted purines were prepared after deprotection of the corresponding THP-derivatives. None of the final purines 2xyz showed any considerable cytostatic activity (L1210, HL60, HeLa S3 and CCRF-CEM cell-lines).

Table 2: Deprotection of 9-THP-purines 1xyz

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Compd</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1aab</td>
<td>2aab</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>1aab</td>
<td>2abb</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>1bbb</td>
<td>2bbb</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>1aca</td>
<td>2aca</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>1bcb</td>
<td>2bcb</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>1cbb</td>
<td>2cbb</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>1ccb</td>
<td>2ccb</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>1cab</td>
<td>2cab</td>
<td>94</td>
</tr>
<tr>
<td>9</td>
<td>1cbb</td>
<td>2cbb</td>
<td>88</td>
</tr>
</tbody>
</table>

* * Isolated yields after crystallization.

Table 3: Characteristic $^{13}$C Chemical Shifts ($\delta$) of CH$_3$ or i-C$_{arom}$ Carbons at Different Positions of the Purine Ring

<table>
<thead>
<tr>
<th>Compound</th>
<th>CH$<em>3$ or i-C$</em>{arom}$ in Position, $\delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>19.35</td>
</tr>
<tr>
<td>6</td>
<td>16.49</td>
</tr>
<tr>
<td>8</td>
<td>16.39</td>
</tr>
</tbody>
</table>

* Chemical shifts of CH$_3$ groups are in normal type, shifts of i-C$_{arom}$ are in *italics.*

Unless otherwise stated, solvents were evaporated at 40°C/2kPa and compounds were dried at 60°C/2kPa. Melting points were determined on a Kofler block and are uncorrected. Mass spectra were measured on Bruker Avance 500 MHz spectrometer (1H at 500, $^{13}$C at 125.7 MHz) and Bruker Avance 400 MHz spectrometer (1H at 400, $^{13}$C at 100.6 MHz). Chemical shifts (in ppm, $\delta$ scale) were referenced to TMS as internal standard; coupling constants (J) are given in Hz. H,C-HMBC and DPPG-NOE experiments were performed for complete assignment of all signals and to verify the position of substituents.

2,6,8-Trichloro-9-(tetrahydropyran-2-yl)purine (1aaa)

LDA (2 M solution in heptane–THF–benzene, 7 mL, 14 mmol) was added dropwise to a stirred solution of 2,6-dichloro-9-(tetrahydro-2-yl)purine (2.75 g, 10 mmol) in THF (40 mL) under argon at –78°C during 30 min and the solution was stirred at –78°C for 1 h. Then a solution of hexachloroethane (5 g, 21 mmol) in THF (40 mL) was added dropwise and stirring at –78°C was continued for 2 h. Then sat. aq NH$_4$Cl (4 mL) was added and after 5 min, the organic phase was separated. It was evaporated and co-distilled with tolune. The residue was chromatographed on a silica gel column (200 g, EioAc–heptane, 1:4 to 1:1) to give the product that was recrystallized from CH$_2$Cl$_2$–heptane; yield: 1.6 g (52%); yellowish crystals; mp 114–116°C (Lit.22 mp 117–119°C).

$^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.61–1.96 (m, 4 H, CH$_2$), 2.15 and 2.90 (2 m, 2 $\times$ 1 H, CH$_2$), 3.74 (td, 1 H, $J$ = 11.8, 2.3 Hz, bCH$_2$O), 4.19 (ddd, 1 H, $J$ = 11.8, 4.9, 1.9 Hz, aCH$_2$O), 5.74 (dd, 1 H, $J$ = 11.4, 2.5 Hz, OCH).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 23.02, 24.48 and 28.68 (CH$_3$), 69.28 (CH$_2$O), 84.25 (OCH), 129.48 (C-5), 144.47 (C-8), 150.39 (C-6), 152.96 (C-2), 153.30 (C-4).

FAB-MS: $m/z$ (%) = 307 (100, M + H$^+$).
Dowex 50 X 8 (H+) (ca. 300 mg), EtOH (50 mL) and H2O (1 mL)

Method E
Cleavage of THP-Protected Purines

was stirred under argon at 75 °C for 8 h. After cooling to r.t., the sol-

product was added dropwise to a stirred solution of a chloropurine (1 mmol) and Fe(acac)3 (103 mg, 0.33 mL, 1 mmol up to 4 mL, 12 mmol) was added dropwise to a stirred solution of a chloropurine (1 mmol), K3PO4 (300 mg, 1.4 mmol), phenylboronic acid (amounts from 122 mg, 1 mmol up to 732 mg, 6 mmol) and Pd(PPh3)4 (59 mg, 0.05 mmol) and the mixture was stirred under argon at 100 °C for 8 h. After cooling to r.t., the sol-

was refluxed for 1 h, then filtered while hot and the resin was washed with hot EtOH (2 × 50 mL). The combined filtrates were

EI-MS: \( m/z \) (-%) = 286 (2, M+), 203 (8), 85 (100).

EI-HRMS: \( m/z \) calc'd for C11H9Cl2N4O: 286.0392; found: 286.0391.

EI-HRMS: \( m/z \) calc'd for C12H15ClN4O: 266.0934; found: 266.0915.

EI-HRMS: \( m/z \) calc'd for C12H15ClN4O: 266.0934; found: 266.0932.

EI-HRMS: \( m/z \) calc'd for C13H18N4O: 246.0876; found: 246.0877.

EI-HRMS: \( m/z \) calc'd for C13H18N4O: 246.0876; found: 246.0874.

EI-HRMS: \( m/z \) calc'd for C13H18N4O: 246.0876; found: 246.0875.

EI-HRMS: \( m/z \) calc'd for C13H18N4O: 246.0876; found: 246.0874.

EI-HRMS: \( m/z \) calc'd for C13H18N4O: 246.0875; found: 246.0876.

EI-HRMS: \( m/z \) calc'd for C13H18N4O: 246.0876; found: 246.0876.

EI-HRMS: \( m/z \) calc'd for C13H18N4O: 246.0876; found: 246.0877.

EI-HRMS: \( m/z \) calc'd for C13H18N4O: 246.0876; found: 246.0875.

EI-HRMS: \( m/z \) calc'd for C13H18N4O: 246.0876; found: 246.0877.

EI-HRMS: \( m/z \) calc'd for C13H18N4O: 246.0875; found: 246.0876.

EI-HRMS: \( m/z \) calc'd for C13H18N4O: 246.0876; found: 246.0877.

EI-HRMS: \( m/z \) calc'd for C13H18N4O: 246.0875; found: 246.0876.
H NMR (400 MHz, CDCl3): δ = 1.56–1.70 (m, 2 H, CH2), 1.76–1.94 (m, 2 H, CH2), 2.09 and 3.32 (2 m, 2 × 1 H, CH2), 3.74 (td, 1 H, J = 12.4, 2.3 Hz, bCH2O), 4.29 (ddt, 1 H, Jgem = 12.4 Hz, J = 5.0, 1.6 Hz, aCH2O), 5.70 (dd, 1 H, J = 11.3, 2.4 Hz, OCH), 7.45–7.62 (m, 9 H, 3 × m- and p-H-Ph), 7.99 (m, 2 H, o-H-Ph), 8.02 (m, 2 H, o-H-Ph). 4,02 (m, 2 H, o-H-Ph). 1H NMR (400 MHz, CDCl3): δ = 1.65–1.91 (m, 3 H, CH2), 2.01, 2.15 and 2.58 (3 m, 3 × 1 H, CH2), 2.84 (s, 3 H, CH3–8), 3.80 (td, 1 H, J = 11.7, 2.5 Hz, bCH2O), 4.23 (ddt, 1 H, Jgem = 11.7 Hz, J = 4.3, 1.9 Hz, aCH2O), 5.97 (dd, 1 H, J = 11.3, 2.4 Hz, OCH), 7.42–7.63 (m, 6 H, 2 × m- and p-H-Ph), 8.65 (m, 2 H, o-H-Ph), 8.90 (m, 2 H, o-H-Ph). 1H NMR (400 MHz, CDCl3): δ = 1.65–1.84 (m, 8 H, CH2), 1.95, 2.10 and 2.33 (3 m, 3 × 1 H, CH2), 2.83 (s, 3 H, CH3–8), 3.76 (td, 1 H, J = 11.8, 2.6 Hz, bCH2O), 4.20 (ddt, 1 H, Jgem = 11.8 Hz, J = 4.4, 1.9 Hz, aCH2O), 5.88 (dd, 1 H, J = 11.3, 2.6 Hz, OCH), 7.49–7.58 (m, 3 H, 3 × m- and p-H-Ph), 8.74 (m, 2 H, o-H-Ph). 13C NMR (100.6 MHz, CDCl3): δ = 12.4, 12.83, 128.63, 128.68 (CDCl3), 129.82 (C-5), 129.90 and 129.99 (CH-Ph), 130.31 (i-C-Ph-8), 130.60 and 130.62 (CH-Ph), 136.37 (i-C-Ph-6), 135.63 (C-6), 151.12 and 155.50 (C-8 and C-4), 157.99 (C-2). EI-HRMS: m/z calc for C16H14Cl2N4O: 308 (12, M+), 224 (100), 183 (20), 85 (16). EI-MS: m/z (%) = 308 (12, M+), 224 (100), 183 (20), 85 (16). 1C NMR (100.6 MHz, CDCl3): δ = 16.26 (CH2-8), 19.63 (CH2-6), 23.27, 25.04 and 30.17 (CH3), 69.01 (CH2O), 82.70 (OCH), 128.13 (m-CH-Ph), 128.35 (o-CH-Ph), 129.68 (p-CH-Ph), 130.53 (C-5), 138.45 (i-C-Ph), 152.32 (C-4), 153.26 (C-8), 156.95 (C-6), 157.96 (C-2). EI-HRMS: m/z (%) = 308 (14, M+), 224 (100), 85 (12). 1C NMR (100.6 MHz, CDCl3): δ = 16.26 (CH2-8), 19.63 (CH2-6), 23.27, 25.04 and 30.17 (CH3), 69.01 (CH2O), 82.70 (OCH), 128.13 (m-CH-Ph), 128.35 (o-CH-Ph), 129.68 (p-CH-Ph), 130.53 (C-5), 138.45 (i-C-Ph), 152.32 (C-4), 153.26 (C-8), 156.95 (C-6), 157.96 (C-2). EI-HRMS: m/z (%) = 308 (14, M+), 224 (100), 85 (12). 8-Methyl-2,6-diphenyl-9-(tetrahydropyran-2-yl)purine (1cbb) Colorless oil.
2.6.8-Trimethylpurine (2bbb)
Colorless crystals from EtOAc–heptane; mp 209–211 °C (Lit.24 mp 220–222 °C).

1H NMR (400 MHz, CDCl3 + MeOD): δ = 2.63 (s, 3 H, CH3-8), 2.73 (s, 3 H, CH3-2), 2.76 (s, 3 H, CH3-6), 2.87 (s, 3 H, CH3-2), 7.42–7.53 (m, 3 H, m- and p-H-PH), 8.52 (br m, 2 H, o-H-PH), 8.84 (br m, 2 H, o-H-PH-6). Anal. Calcld for C18H14N4: 286.1218; found: 286.1212.

13C NMR (100.6 MHz, CDCl3 + MeOD): δ = 13.99 (CH3-8), 128.06, 128.46, 128.50, 129.58, 129.85 and 130.55 (CH-PH), 136.12 (i-C-PH-6), 138.38 (i-C-PH-2), 152.66 (C-6), 153.99 (C-8), 155.08 (C-4), 157.90 (C-2). Note: C-5 signal did not appear.
EI-MS: m/z (%) = 224 (100, M+), 209 (5), 193 (6). EI-HRMS: m/z calculated for C18H14N4: 286.1206; found: 286.1212.

2-Chloro-8-methyl-6-phenylpurine (2acb)

1H NMR (400 MHz, CDCl3 + MeOD): δ = 2.63 (s, 3 H, CH3-8), 7.45–7.63 (m, 6 H, m- and p-H-PH), 8.52 (br m, 2 H, o-H-PH-2), 8.84 (br m, 2 H, o-H-PH-6).

13C NMR (100.6 MHz, CDCl3 + MeOD): δ = 13.99 (CH3-8), 128.06, 128.46, 128.50, 129.58, 129.85 and 130.55 (CH-PH), 136.12 (i-C-PH-6), 138.38 (i-C-PH-2), 152.66 (C-6), 153.99 (C-8), 155.08 (C-4), 157.90 (C-2). Note: C-5 signal did not appear.
EI-MS: m/z (%) = 224 (100, M+), 209 (5), 193 (6). EI-HRMS: m/z calculated for C18H14N4: 286.1206; found: 286.1212.

Acknowledgment
This work is part of research project Z4 055 905. It was supported by the Grant Agency of the Academy of Sciences of the Czech Republic (grant No. B4055201) and by Sumika Fine Chemicals, Co. Ltd. (Osaka, Japan). The authors also thank Mrs. Kamila Havlikova for technical assistance and Dr. Ivan Votrubova for cytostatic activity screening.

References


